Adaptive (T and B cell) Immunity and Control by Dendritic Cells in Atherosclerosis

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Abstract

Chronic inflammation in response to lipoprotein accumulation in the arterial wall is central in the development of atherosclerosis. Both innate and adaptive immunity are involved in this process. Adaptive immune responses develop against an array of potential antigens presented to effector T lymphocytes by antigen-presenting cells, especially dendritic cells. Functional analysis of the role of different T cell subsets identified the Th1 responses as proatherogenic, whereas regulatory T cell responses exert antiatherogenic activities. The impact of Th2 and Th17 responses is still debated. Atherosclerosis is also associated with B-cell activation. Recent evidence established that conventional B-2 cells promote atherosclerosis. In contrast, innate B-1 B cells offer protection through secretion of natural IgM antibodies. This review discusses the recent development in our understanding of the role of T- and B-cell subsets in atherosclerosis, and addresses the role of dendritic cell subpopulations in the control of adaptive immunity.

Key Words
T lymphocytes, B lymphocytes, Dendritic Cells, antibodies, cardiovascular disease

Abbreviation List
APC: antigen presenting cell
BATF3: Basic leucine zipper transcription factor ATF-like 3
BST-2: bone marrow stromal cell antigen-2
cDC: classical dendritic cell
CTLA-4: Cytotoxic T-Lymphocyte Antigen 4
CVD : cardiovascular disease
DAMP: damage-associated molecular pattern
DC-SIGN: Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin
DC: dendritic cell
FcγR: Fc gamma receptors
Flt3: Fms-like tyrosine kinase 3
FoxP3: Forkhead/winged helix transcription factor
GATA:
GM-CSF: granulocyte-macrophage colony-stimulating factor
Hsp: Heat shock ptptein
ICOS: Inducible T-cell COStimulator
Id3: Inhibitor of DNA binding 3
IDO: indoleamine 2,3-dioxygenase
IFN-γ: Interferon- γ
IL-17R: IL-17 receptor
IL: Interleukin
ILC: innate lymphoid cell
IRA B cell: innate response activator B cell
LPS: lipopolysaccharide
LT□□□□lymphotoxin □
MDA-LDL: malondialdehyde-LDL
MHC: major histocompatibility complex
MIF :migration inhibitory factor
MZ: Marginal Zone
NH: Natural helper
NK natural killer
NLR: NOD-like receptor
oxLDL: oxidized LDL

PAMP: pathogen-associated molecular pattern
PD-1: Programmed cell death 1
pDC: plasmacytoid DC
RAG: recombination-activating protein
RLR: RIG-I-like receptor
ROR: Retinoic-acid-receptor-related orphan receptor
RUNX1: Runt-related transcription factor 1
SCID: severe combined immunodeficiency
SOCS/ Suppressor of Cytokine Signaling
STAT: signal transducer and activator of transcription
T-bet: T-box expressed in T cell
TBX: T-box transcription factor
Tcf4 : Transcription factor 4
TCR: T cell receptor
TGF-β: Transforming growth factor- β
TLO: tertiary lymphoid organ
TLR: Toll-like receptor
TNF-α: Tumor necrosis factor- α
Treg cell: regulatory T cell
VH: heavy chain V
Zbtb46: Zinc Finger And BTB Domain Containing 46
α-Galcer: α-galactosylceramide

I. Introduction

In his article celebrating the 100th anniversary of the discovery in 1913 of the key role of cholesterol in the pathogenesis of atherosclerosis by Nikolai N. Anitschkow, Daniel Steinberg reminds us that the young Russian experimental pathologist from Saint Petersburg had already anticipated that inflammation might play a role in lesion development [1]. If, nowadays, there is no doubt that cholesterol is the initiating factor that causes the response to injury leading to atherosclerosis, it is also now well-established and accepted that the complex molecular and cellular mechanisms that underlie the development and progression of atherosclerotic lesions following sub-endothelial lipoprotein accumulation have all the features of those responsible for chronic inflammatory diseases.

Inflammation is an integral part of both innate and adaptive immunity. It consists of a complex series of interactions between soluble mediators and cellular effectors that occur in response to pathogens or tissue injury, as is the case in atherosclerosis. The innate immune response is comprised of a range of soluble factors, including complement proteins, and several cellular effectors, including granulocytes, mast cells, macrophages, dendritic cells (DCs), natural killer (NK) cells, innate lymphoid cells (ILC) and B-1 cells (Figure 1). Innate immunity is genetically fixed and relies on a defined set of receptors, including germline-encoded Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptor (RLRs), C-type lectin and scavenger receptors that recognize pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), the latter being involved in atherogenesis. A number of excellent reviews have recently been published on the role of innate immunity in atherosclerosis [2-4]. In contrast, adaptive immunity is antigen-specific, and relies on a large pool of T (CD4+ and CD8+) and B cells expressing antigen receptors whose repertoire is created by the somatic recombination of different germline-encoded gene segments. These receptors are specific for either microbial derived proteins or processed peptides that are presented in association with either class I or class II major histocompatibility complex (MHC). NKT cells and γδ T cells are cytotoxic T lymphocytes that function at the intersection of innate and adaptive immunity and can recognize lipid and other molecular antigens as well as proteins (Figure 1). Several reviews have recently addressed the role of adaptive immunity in atherosclerosis [2, 5-8]. In this review we will discuss the evidence supporting a role of the different components of the adaptive immune system and its control by DCs in atherosclerosis in light of the available data from human and animal model studies.

II. Role of T cells in atherosclerosis

II.1. Experimental evidence

The first evidence that pointed to a role of adaptive immunity in atherosclerosis was the widespread expression of the MHC class II, HLA-DR, in human atherosclerotic plaques [9], and the presence of a large number of $CD3^+$ T cells in atherosclerotic plaques in humans [10] as well as in mice [11, 12]. The majority of T cells in mouse and human atherosclerotic plaques are $CD4^+$ T-helper cells expressing the αβ T-cell antigen receptor (TCR). $CD8^+$ T cells are also present in human atherosclerotic plaques [13], but sparse in mouse lesions [12]. T lymphocytes are among the earliest cells to be recruited in the atherosclerotic plaque [14]. Altogether these early observations on the presence of T cells in human and mouse atherosclerotic plaques remained associative, and did not show causation.

Subsequent studies using animal models of atherosclerosis, especially $Apoe^{-/-}$ or $Ldlr^{-/-}$ mice, in which human-like atherosclerotic lesions develop spontaneously or in response to high fat diet, provided more direct evidence for the participation of adaptive immunity in atherogenesis. $Apoe^{-/-}$ or $Ldlr^{-/-}$ mice crossed with immunodeficient mice that lack the V(D)J recombination-activating protein 1 RAG1 ($Rag1^{-/-}$) or 2 ($Rag2^{-/-}$), or have a severe combined immunodeficiency (SCID) mutation (scid/scid mice) show, in general, reduced development of atherosclerotic lesions when fed a chow diet (reviewed in [5]). These immunodeficient mice that

lack both T and conventional B cells are not particularly informative on the role of specific T and B cell subpopulations that can be either pro- or anti-atherogenic (see below). One study found no difference between immune-competent and –deficient mice fed a high fat diet [15].

The specific role of T cells was substantiated by experiments showing that the transfer of CD4+ T cells into scid/scid/Apoe$^{-/-}$ mice fully reversed the atheroprotection provided by T/B deficiency [16]. However, when the effect of CD4+ T cells was evaluated in CD4-deficient Apoe$^{-/-}$ mice, contrasting results were reported. Female CD4$^{-/-}$Apoe$^{-/-}$ mice exhibited markedly larger lesions in the descending thoracic aorta, but no effect was observed in the aortic root, as compared with wild type Apoe$^{-/-}$ mice [17]. Intriguingly, in a subsequent study using the same CD4/Apoe double knockout mice, atherosclerosis in the aortic sinus was reduced, but the authors made no mention of the effect of CD4+ T cell deficiency on atherosclerosis in the aorta [18]. Of note, in both studies, the CD8+ cell population and the titers of anti MDA-oxidized LDL (oxLDL) IgM antibodies were increased. CD8+T cells were recently shown to promote the development of vulnerable atherosclerotic plaques [19], whereas natural anti-oxLDL IgM autoantibodies are atheroprotective (reviewed in [20]; see below).

The specific recognition of peptide antigens presented by MHC molecules triggers TCR signaling, but co-stimulatory and co-inhibitory receptors on T cells direct T cell function and determine T cell fate. These co-signaling molecules are members of the immunoglobulin superfamily, including B7(CD80/86), CD28, PD-1 and CTLA-4, and the tumor necrosis factor receptor superfamily, including CD40, CD27, OX40, and CD137. Experiments aimed at investigating the role of co-signaling molecules provided further evidence for a role of T cells in atherogenesis (reviewed in [21, 22], see below IV.2). For example, blockade of the OX40-OX40L interaction by anti-OX40L antibody treatment in Ldlr$^{-/-}$ [23] or Apoe$^{-/-}$ mice [24] reduced atherosclerosis. Yet, blockade of T cell activation was accompanied by an enhanced B-1 cell activity and increased atheroprotective anti-oxLDL natural IgM antibodies. This was also the case in Ldlr$^{-/-}$ mice deficient in CD74, a membrane chaperone that regulates antigen presentation and T-cell activation by associating with MHC class II molecules, but also serves as cell surface receptor for macrophage migration inhibitory factor (MIF) [25]. The expression of several co-signaling molecules is not exclusively confined to adaptive immune cells and thus global knockout models can also impact both innate immune and vascular cell activation. For instance, CD40 is widely expressed on non-hematopoietic cells, including endothelial cells, fibroblasts, and epithelial cells [26] as well as on platelets, and CD137 is expressed by endothelial and smooth muscle cells [27].

The specificity of the T-cell response in atherosclerosis is a complex issue. The inflammatory process that prevails in the plaque might promote the recruitment of heterogeneous polyclonal T cells. However, analysis of T cells derived from Apoe$^{-/-}$ mice showed a highly restricted TCR$\alpha\beta$-repertoire pointing to a specific antigen-driven process [28], and TCRβ deficiency in Apoe-/- mice has been shown to be atheroprotective [17]. T cells isolated and cloned from human plaques respond to oxLDL in a MHC class II (HLA-DR)-restricted manner [29], making oxLDL the principal candidate antigen in atherosclerosis. In support of this, the transfer of T cells sensitized to oxLDL into scid/scid/Apoe$^{-/-}$ mice accelerated atherosclerotic lesion development [16]. T-cells isolated from human early atherosclerotic lesions (iliac arteries) or late lesions (common carotid) also react to Heat shock protein (Hsp)60 and recognize Hsp60-derived peptides [30]. However, transfer of effector T-cells recognizing antigens not specific to atherosclerosis can also be proatherogenic: CD4$^+$ T cells from systemic lupus erythematous (SLE)-susceptible mice transferred into Ldlr$^{-/-}$ mice increased atherosclerosis [31]. SLE autoantigens are most often those of nuclear origin, thus supporting a potential role for nucleus-derived autoantigens in atherosclerosis as well as SLE. Also, patients with autoimmune disorders, such as rheumatoid arthritis [32], SLE [33] or psoriasis [34], have an increased risk of cardiovascular disease (CVD). This co-morbidity cannot be accounted for by traditional cardiovascular risk factors, and further supports evidence that atherosclerosis shares similar disease mechanisms with these autoimmune disorders, including dysregulation of the adaptive immune system.

Altogether, it is clear that the adaptive immunity is activated and participates in atherosclerosis, but some points are often neglected. Modulation of T, B and DC numbers has complex effects

on lipoprotein metabolism, which might directly influence atherosclerosis. Total plasma cholesterol levels were significantly lower in Rag2$^{-/-}$ Apoe$^{-/-}$ mice [35], as compared with immunocompetent mice. Similarly, LDL cholesterol levels were slightly lower in CD74$^{-/-}$ Ldlr$^{-/-}$ mice that are deficient in T cells [25]. As a result, part of the atheroprotection offered by T cell depletion or deactivation of the immune system might be elicited by a reduction in cholesterol levels. The lipoprotein and plasma lipid differences in immunodeficient mice are likely due to the reduced inflammatory status of these mice and altered spectrum of pro-inflammatory cytokines, which affect lipoprotein metabolism and/or catabolism [36]. Also, the roles played by the adaptive immunity are site-specific and time-dependent in animal models, which likely also holds true for humans. No differences in lesions were observed in the brachiocephalic artery whereas in the aortic sinus of immune-deficient mice the lesions were smaller as compared with immunocompetent Apoe$^{-/-}$ mice [35]. Moreover, T cells seem to play a rather minor role in advanced lesion growth in mice: atherosclerosis in the aortic sinus was reduced in immune-deficient Apoe$^{-/-}$ mice fed a chow diet but not in those fed a Western diet [15, 37], and early lesions (8 weeks) were smaller in Rag1-deficient Ldlr$^{-/-}$ mice but late lesions (16 weeks) did not show any significant difference [38]. Although understanding plaque growth is critical to better understanding disease etiology, causes of plaque stability and rupture are a more immediate target clinically. This is much harder to model in animals, although several protocols exist [39], but evidence in human atherosclerosis suggest an important association of infiltrated T cells with unstable plaques. Unstable plaques are associated with immune-inflammatory features including increased levels of T cells [40] and DCs [41].

II. 2. T cell subsets

Upon engagement of their TCR with the antigen-MHC complex displayed on the surface of an antigen presenting cell (APC), naïve CD4$^+$ T lymphocytes differentiate into various effector or regulatory subsets, depending on the specific micro environment of co-signaling and cytokines (Figure 2). These cells elicit distinct functions and display specific profiles of cytokine production.

Th1 cells

For a long time, it was believed that naïve CD4$^+$ T cells polarize towards either Th1 or Th2 lymphocytes according to mutually exclusive differentiation programs. Th1 commitment is mainly triggered by IFN-γ and IL-12. Terminally differentiated Th1 cells are characterized by the expression of the transcription factor T-box transcription factor (TBX)-21 (also referred to as T-bet) and the production of IFN-γ. IL-12 triggers the two key lineage defining transcription factors: signal transducer and activator of transcription (STAT-4) and T-bet. In turn, T-bet induces the production of IFN-γ and the expression of the high affinity IL-12 receptor, while down regulating the expression of IL-4 and IL-5, characteristic of type 2-dominated responses. Th1 cells are generally involved in immunity against intracellular pathogens, but have also been implicated in several autoimmune and inflammatory diseases including atherosclerosis. Th1 are the most abundant T-cell subtype in human atherosclerotic plaques [42]. They exhibit signs of activation; they secrete cytokines such as IFN-γ, TNF-α and IL-2, and may proliferate in situ [43]. The hallmark cytokine produced by Th1 cells, IFN-γ, can exert diverse pro-atherogenic actions (reviewed in [43, 44]). IFN-γ activates macrophages and DCs, which improves the efficiency of antigen presentation and promotes further Th1 polarization. Genetic deficiency in IFN-γ or its receptor in Apoe-/- mice reduced lesion formation and enhanced plaque stability via increased collagen content [45], whereas exogenously administered IFN-γ accelerated atherosclerosis [46]. Intriguingly, it seems that the protective effect of IFN-γ deficiency is restricted to male mice [47]. Pro-inflammatory effects of IFN-γ are mainly mediated through activation of the transcription factor STAT-1. Consistently, chimeric mice generated by bone marrow transplantation from STAT-1-deficient Apoe$^{-/-}$ mice into Apoe$^{-/-}$ mice displayed reduced lesion formation [48, 49]. These animal studies have been widely used to demonstrate that atherosclerosis is a Th1-driven inflammatory disease. However, although IFN-γ expression is restricted to lymphoid cells in mice, it is not only produced by Th1 cells, but also by NKT and NK cells as part of the innate immune response. NKT cells have been shown to be

proatherogenic (see below). The role of NK cells remains relatively unexplored and controversial [50, 51].

IL-12 produced by DCs is essential for Th1 differentiation and induction of T-bet. Interestingly, exogenous administration of IL-12 augmented IFN-γ levels in the aorta and accelerated atherosclerosis [52]. However, Apoe$^{-/-}$ mice deficient in IL-12 showed a marked reduction in atherosclerosis, which was only evident in early stages but not in more advanced lesions [53], reminiscent of what is observed in immunodeficient mice. Yet, because these mice were deficient in IL12p40, the common subunit of IL-12 and IL-23, a role for IL-23 cannot be ruled out.

In addition to IL-12, IL-18 also promotes T-bet expression and subsequent Th1 cell development. Injection of IL-18 accelerated atherosclerosis [54], while treatment of Apoe$^{-/-}$ mice with a plasmid encoding an endogenous IL-18 inhibitor significantly reduced atherosclerosis [55]. Furthermore, IL-18 deficient Apoe$^{-/-}$ mice showed a marked reduction of atherosclerotic lesions and diminished Th1 cell activity, as illustrated by a switch from Th1 related antibody isotypes IgG2a to Th2 related antibody isotypes IgG1 [56].

The Th1/Th2 switch has been widely used to ascertain the proatherogenic effect of Th1 and the anti-atherogenicity of Th2. Indeed, deficiency of T-bet in Ldlr$^{-/-}$ mice, which causes a switch to Th2 and a change in antibody responses, reduced lesion development [57]. Also Apoe$^{-/-}$ mice on a BALB/c background, which display predominant Th2 responses, showed reduced atherosclerotic lesions at all time points studied [58]. Other genetic manipulations were used to investigate the effect of Th1/Th2 switch on atherosclerosis. Transgenic C57BL/6 mice with changes in MHC class II antigens to decrease Th1 and increase Th2 expression under high fat diet containing cholate displayed smaller atherosclerotic lesions than wild type mice [59]. Moreover, BALB/c mice deficient in STAT-6, which mount dominant Th1-cell responses developed atherosclerotic lesions comparable to C57BL/6J mice on the same diet [59, 60]. All these findings were often interpreted as evidence for an antiatherogenic effect of Th2 responses, when in fact they demonstrate that a Th1/Th2 switch alleviates the proatherogenic effects of Th1. In the case of T-bet deficiency studies, a note of caution is that T-bet is also expressed by type 1 innate lymphoid cells (ILC1), including NK cells [61].

Th2 cells

Th2 differentiation is induced by DCs through IL-6 and IL-13 secretion and OX40-OX40L interaction [62]. Th2 cells play an essential role in B cell-mediated humoral responses, especially against extracellular pathogens. They secrete IL-4, IL-5, and IL-13, and can also produce IL-10. Yet, IL-10 is mostly produced by macrophages, and regulatory T and B cells. IL-5 and IL-13 are also not exclusive to adaptive T cells and can be abundantly secreted by ILC2 [61]. STAT-6 activation by IL-4 induces expression of the master Th2 differentiation transcription factor GATA-3 [63], which upregulates IL-4 and IL-5, and inhibits the production of IFN-γ. Consequently, Th2 cells might counteract the pro-atherogenic Th1 effects. Yet, GATA-3 is also important in ILC2 [64] and ILC3 [65] differentiation.

Recent data have shown that IL-9 is produced by a newly defined T cell subpopulation, Th9 cells that are reprogrammed from Th2 by TGF-β [66]. Patients with acute myocardial infarction have increased IL-9 plasma levels, and carotid atherosclerotic plaques display increased mRNA levels of IL-9 and IL-9 receptor as compared with normal vessels [67]. Further studies are required to elucidate the role of IL-9 and Th9 in atherosclerosis.

As seen above, the role of Th2 in atherosclerosis is rather difficult to establish in a straightforward manner. In particular, if Th2 cells were anti-atherogenic, deficiency in IL-4, the prototypical Th2 cytokine, should result in accelerated atherosclerosis. In contrast, Ldlr$^{-/-}$ transplanted with bone marrow from IL-4 deficient mice showed reduced atherosclerosis in a site-specific manner, compared to mice transplanted with IL-4 competent bone marrow [68]. Similar results were documented in Apoe$^{-/-}$ mice lacking IL-4, suggesting a pro-atherogenic role of Th2 [53]. However, in a second study the exogenous administration or genetic deficiency of IL-4 had no effect on lesion development in both hypercholesterolemic and angiotensin II induced atherosclerosis [69]. Overall, these studies that evaluated the effect of IL-4 deficiency on atherosclerosis suggest that the lack of Th2 responses does not promote atherosclerosis,

and may even be protective. Yet, a not of caution should be sounded here, since IL-4 is also made by mast cells, and mast cells contribute to atherosclerosis [70].
Another prototypical Th2 cytokine is IL-13, which is also produced by other cell types, including NK cells, eosinophils, basophils, mast cells, macrophages [71] and ILC2 [61]. Its effect on atherosclerosis has been recently investigated. Chimeric $Ldlr^{-/-}$ mice transplanted with bone marrow from $IL\text{-}13^{-/-}$ mice developed larger atherosclerotic lesions than $Ldlr^{-/-}$ mice reconstituted with wild type bone marrow, which was associated with a selective decrease in IL-4 and IL-10, no change in IL-5 and IFN-γ production and a significant increase in Th1-dependent IgG2c antibodies in serum [72]. Moreover, IL-13 administered to $Ldlr^{-/-}$ mice for a short period of time at a dose that did not modify the Th1/Th2 balance had no effect on plaque size, but lesions were more stable and less inflammatory, which highlights the pro-fibrotic and anti-inflammatory properties of IL-13, independently of its effect on the adaptive immune system.
IL-19, a member of the IL-10 family of cytokines, produced by monocytes and other non-immune tissue cells under inflammatory conditions, has been shown to polarize the T cell response towards Th2 [73]. IL-19 decreased atherosclerosis in $Ldlr^{-/-}$ or $Apoe^{-/-}$ mice, and the expression of the Th1 markers T-bet and IFN-γ was reduced in splenocytes from mice injected with IL-19 [74].
Several studies support a protective role of IL-5 producing Th2 cells in atherosclerosis. MDA-modified LDL vaccination of $Apoe^{-/-}$ mice reduced atherosclerosis via secretion of IL-5 and increased production of anti-oxLDL IgM antibodies, while IL-5 deficiency inhibited the protective effect of vaccination by blocking the production of anti-oxLDL antibodies [75]. Moreover, blockade of IL-5 by neutralizing anti-IL-5 antibodies abolished the atheroprotective effect of IL-33 administration in $Apoe^{-/-}$ mice, which was associated with increased production of Th2 cytokines and anti-oxLDL IgM antibodies [76]. Even though these studies highlighted the anti-atherogenic properties of IL-5, they did not clearly identify the source of IL-5 as Th2 cells. Interestingly, the natural immunity associated with the production of atheroprotective anti-oxLDL IgM was impaired in Apoe-/- mice deficient in Id3 due to reduced IL-5, resulting in increased atherosclerosis [77]. However, IL-5 was not generated from Th2 or mast cells, but from natural helper (NH) cells, a subset of ILC2 [77, 78]. ILC2 include NH cells, multi-potent progenitor type 2 cells, nuocytes or innate type 2 helper cells [61] They are RORγ-independent, and require Id2, IL-7, RORα, and the common cytokine receptor γ-chain for their development. They produce Th2 cytokines, most notably IL-5 and IL-13, but not IL-4, in response to IL-25 and IL-33. The role of ILCs in atherosclerosis needs to be explored.
In conclusion, most of the studies that highlighted the anti-atherogenic effect of Th2 cells were biased by the concomitant decrease in Th1 responses or did not definitely identify the source of type 2 cytokines as Th2 cells and not ILC2.

Th17 cells
In recent years, Th17 cells have emerged as a new $CD4^+$ T cell subset, leading to a revision of the Th1/Th2 paradigm. Differentiation of naïve T cells into Th17 requires the nuclear receptor ROR-γt and depends on other transcription factors, including ROR-α, STAT-3, Aryl hydrocarbon receptor, and runt-related transcription factor 1 (RUNX1) [79]. Th17 cells produce large quantities of IL-17A and exhibit effector functions distinct from Th1 and Th2 lymphocytes. In addition to the signature cytokine IL-17A, Th17 cells produce IL-17F, IL-22 and IL-23. TGF-β and IL-6 are necessary for Th17 differentiation, while IL1-β is instrumental for human Th17 development. IL-21 and IL-23 are required for Th17 proliferation and maintenance, respectively. IL-23 stabilizes the inflammatory phenotype of Th17 cells [80]. IL-6 activates STAT-3, which is required for ROR-γt expression and function. IL-6 drives the effect of TGF-β toward the development of Th17 cells instead of promoting that of Treg cells [81]. The Th1 transcription factor T-bet might repress Th17 development by blocking the transcription of ROR-γt [82]. Furthermore, Th1 and Th2 cytokines, IFN-γ and IL-4 may directly suppress Th17 differentiation, while IL-17 inhibits Th1 polarization, IFN-γ production and T-bet expression [83]. Recently, a new role for platelet-derived PF4 in blocking Th17 differentiation has been revealed [84].

Th17 cells are important to clear extracellular bacteria and fungi by activating neutrophils through the production of IL-17A and IL-17F. They are also involved in the development of inflammatory bowel diseases, autoimmune diseases such as rheumatoid arthritis and experimental autoimmune encephalomyelitis [85], whereas cytokines secreted by Th17 cells, including IL-22 and IL-23 may restrain inflammatory responses during microbial infection and allergy [86, 87]. Accumulation of Th17 cells and IL-17 has been observed in murine [88-90] and human [88, 91-93] atherosclerotic lesions. The expression of IL-17 in human carotid lesions was associated with a stable plaque phenotype [88, 93], but another study showed a positive correlation of IL-17A expression and plaque instability [92].

The role of IL-17 has been investigated in several mouse models of atherosclerosis, but results are conflicting with pro- and anti-atherogenic effects attributed to Th17 (reviewed in [94]). A pro-atherogenic role of Th17 was suggested in Apoe$^{-/-}$ mice deficient in Fcγ chain, which developed less atherosclerosis, associated with less Th17 cells and reduced IL-17 secretion by activated CD4^{+} T-cells [95]. The protective effect was accompanied by increased Treg cells that produced more TGF-β and IL-10 [95].

Neutralizing experiments with anti-IL-17 antibodies or genetic deficiency of IL-17A in mouse models provided more direct evidence for a role of Th17 in atherosclerosis. Blocking IL-17 with polyclonal anti-IL-17 neutralizing antibodies raised in rats or goats resulted in significant reduction, whereas rIL-17 treatment augmented atherosclerosis in Apoe$^{-/-}$ mice [96, 97]. It is noteworthy that blocking IL-17A in these studies did not alter the signaling pathway, which might be accounted for by the use of polyclonal non-murine antibodies. On the contrary, blockade of IL-17A with mouse monoclonal anti-IL-17A antibodies that abolished IL-17A signaling did not affect atherosclerosis in Ldlr$^{-/-}$ mice that have low levels of IL-17 [88, 98], whereas treatment with rat anti-IL-17A did not abolish IL-17A signaling but reduced atherosclerosis [98]. In Ldlr$^{-/-}$ mice with SOCS3 deletion in T-cells, which specifically promotes T cell polarization toward Th17, IL-17 production was increased and atherosclerosis markedly reduced [88]. Interestingly, in these mice anti-IL-17A treatment with a mouse monoclonal antibody not only blocked the beneficial effect of Th17 polarization but accelerated atherosclerosis beyond that in wild type Ldlr$^{-/-}$ mice [88]. In agreement with this finding, IL-17A was found to induce a stable plaque phenotype in Ldlr$^{-/-}$ mice transplanted with bone marrow from mice with a T cell-specific deletion of Smad7, a potent inhibitor of TGF-β signaling [93]. These mice displayed a Th17 profile, as indicated by the detection of RORγt and increased IL-17A expression in draining lymph nodes [93].

Treatment with adenovirus encoding IL-17 receptor A (IL-17RA) reduced atherosclerosis in Apoe$^{-/-}$ mice [89]. However, no direct evidence for a sustained blockade of IL 17 signaling was reported in this study. Also, Ldlr$^{-/-}$ mice transplanted with bone marrow from mice deficient in IL-17R showed smaller atherosclerotic lesions, associated with decreased mast cells, and reduced IL-6 and increased IL-10 levels [99]. Yet, interpretation of this finding should be done with care, because IL-17R$^{-/-}$ mice have been shown to produce more IL-17A due to the disruption of negative feedback inhibition [100], which means that the anti-atherosclerotic effect of myeloid IL-17R deficiency might be due to increased IL-17A levels, acting on non-hematopoietic cells.

Genetic deficiency in IL-17A in Apoe$^{-/-}$ mice also provided conflicting results that are difficult to explain. Usui et al. observed reduced atherosclerosis in IL17A deficient Apoe-/- mice fed a no cholate/high-fat diet for 12 weeks [101] whereas Danzaki et al. reported exaggerated atherosclerosis in IL17A Apoe-double knockout mice fed similar diet for 8 or 16 weeks, which was associated with increased IFN-γ and decreased IL-5 production by splenic CD4^{+} T-cells [102]; Madhur et al. found no effect in IL17A deficient Apoe$^{-/-}$ mice fed cholate containing high fat diet for 12 weeks [103].

One possible explanation for the contradictory findings reported so far in the literature is that IL-17A is produced not only by T-cells but also by innate γδ T cells and vascular cells, and not only immune cells are targets of IL-17. Therefore, studies with global deficiency in IL-17, treatment with neutralizing anti-IL-17 antibodies or administration of recombinant IL-17 do not allow conclusions on the specific role of Th17 in atherosclerosis. Nevertheless, it seems that in Th1-driven autoimmune diseases, such as atherosclerosis or T-cell induced enterocolitis [83],

IL-17 produced by Th17 cells have beneficial effects by inhibiting Th1 cell activation after binding to IL-17R expressed on Th1 cells and repressing T-bet expression [104]. As a result, pathogenic Th1-associated molecules, such as IFN-γ and IL-12 receptor β2 subunit, are inhibited. In addition, the most recent data indicate that IL-17A promotes collagen synthesis [93, 105], whereas IFN-γ is known to inhibit it [106], which could account for the plaque-stabilizing effect of Th17 cells.
In humans, low levels of IL-17 in patients with acute coronary syndromes were associated with increased risk of death and myocardial infarction [107]. Data in mice and humans reveal a critical contribution of Th17-associated cytokines, IL-23 and IL-17, in rheumatoid arthritis and psoriasis. Anti-IL 17 and anti IL-12/23p40 antibody therapy is currently under evaluation in this setting. Given the potentially adverse effects of IL-17 blockade in atherosclerosis, a note of caution should be considered when treating patients with inhibitors of the IL-17 pathway.

Treg cells
Several subsets of CD4+ T cells with immunosuppressive activity have been described. The naturally occurring regulatory T (Treg) cells are generated during T cell development in the thymus, while induced Treg (iTreg) cells can be generated in the periphery from naïve CD4+ T cells. Treg cell generation essentially depends on TGF-β, together with TCR costimulatory signals (mainly CTLA-4 on Treg with CD80/86 on APCs), and IL-2. Treg cells express the forkhead/winged helix transcription factor (FoxP3) that is required for their development and functions. Treg cells are essential in the control of autoimmunity and the maintenance of self-tolerance. They are capable of suppressing the activation of effector T-cells, by direct interaction or through inhibition of APCs, resulting in the regulation of both priming and execution of T effector responses. The immune suppressive actions of Treg cells are generally transmitted through cellular contact and/or secretion of the anti-inflammatory cytokines IL-10, TGF-β, and IL-35.
Human atherosclerotic lesions contain only limited Treg cell numbers (1–5% of all T-cells) compared to other chronically inflamed tissues, where up to 25% of T-cells are immunosuppressive T cells [108]. Patients with coronary artery disease (CAD) have reduced peripheral Treg cell numbers, determined as either $CD4^+CD25^+Foxp3^+$ [109], $CD4^+CD25^{high}$ [110] or $CD4^+TGF\text{-}\beta^+$ Th3 cells [111]. Functional properties of Treg cells appear to be compromised in CAD. They expressed less Foxp3 and CTLA4 and exhibited less immune suppressive capacities in vitro [110]. Also, $Apoe^{-/-}$ mice have fewer Treg cells in the spleen and demonstrate impaired Treg cell suppressive function, compared to C57BL/6 mice [112]. Importantly, while local aortic Treg cell levels initially increase, the latter were reduced and the local effector T/Treg cell ratio greatly enhanced after 8-week feeding with high fat diet in $Apoe^{-/-}$ mice [113]. This effect was reversed by switching to a chow diet.
A large body of evidence now exists showing that Treg cells exert a protective role in atherosclerosis. The principal Treg cytokines IL-10 and TGF-β have been shown to induce potent anti-atherogenic activities. Genetic inactivation, or blockade of IL-10 or TGF-β with neutralizing antibodies, aggravated atherosclerosis in mice, with enhanced vascular inflammation and exacerbation of pathogenic Th1 and Th2 responses [114-118]. Yet, these earlier studies did not provide direct evidence for a role of Treg cells in atherosclerosis, since both TGFβ and IL-10 are mainly produced by macrophages. Subsequent studies addressed this issue. Targeted inactivation of TGF-β signaling specifically in T cells markedly enhanced atherosclerosis, suggesting an important role for this cytokine produced by Treg cells in atherosclerosis [119, 120]. Depletion of Treg cells points to a protective role of these cells in atherosclerosis. Significant aggravation of atherosclerosis is observed in mice with reduced Treg cell numbers, achieved by deletion of CD80/86, CD28, ICOS or after treatment with CD25-neutralizing antibodies [121, 122]. Other strategies for Treg cell ablation, including antisense-induced Treg cell apoptosis, vaccination of mice against Foxp3 [123], or use of mice expressing the diphtheria toxin receptor under control of the Treg-specific Foxp3 promoter [124], also lead to increased vascular inflammation and atherosclerosis. It is noteworthy that this latter study is difficult to interpret because Treg depletion increased atherogenic lipoprotein levels. On the contrary, adoptive transfer of $CD4^+CD25^+$ Treg cells [121, 125] or IL-10 producing

Tr1 cells [126] reduced atherosclerotic lesion development in Apoe$^{-/-}$ mice. Similarly, expansion of Treg cells by blocking the chemokine CCL17, whose expression by DCs restrains the homeostasis of Treg cells, reduced the progression of atherosclerosis [127].
Treg cells can directly inhibit the pro-inflammatory phenotype of macrophages resulting in reduced foam cell formation and differentiation of macrophages towards an anti-inflammatory M2 phenotype [128]. They can also directly regulate endothelial cell activation and leukocyte recruitment, independent of their suppressive functions on effector T-cells [113].
Overall, recent studies strongly suggest that the protection by Treg cell-mediated immune tolerance is hampered in atherosclerosis, and that immunomodulatory strategies aimed at the induction of self-tolerance should be able to limit the development of the disease. Induction of peripheral tolerance against selected antigens is currently under evaluation to prevent or treat autoimmune, inflammatory, or allergic diseases [129].

Induction of tolerance in atherosclerosis

Approaches to induce tolerance in the context of atherosclerosis have focused on a few selected antigens, mainly oxLDL, ApoB-100 peptides or Heat shock proteins. Injection of oxLDL at birth to newborn Apoe$^{-/-}$ mice reduced the immune response to oxLDL and the development of atherosclerosis [130]. Nasal, oral or subcutaneous administration of small doses of mycobacterial Hsp65 in Ldlr$^{-/-}$ mice reduced atherosclerotic lesion development [131, 132]. Mucosal administration of oxLDL, Hsp60, or ApoB-100 peptides fused to the B subunit of the cholera toxin (which served as a carrier protein) also attenuated atherosclerosis [133-136]. The induction of tolerance in these models was associated with an increase in Treg cells and TGF-β production, IL-10 production, or both.
Based on the observation that long-term subcutaneous infusion of adjuvant-free, low-dose influenza HA (107-119) peptide transformed mature effector Th cells into CD25^{+} Treg cells [137], we recently reported that subcutaneous infusion of low doses of ApoB-100-derived peptides in Apoe$^{-/-}$ mice for 2 weeks markedly inhibited plaque development and progression [138]. The treatment was associated with a promotion of antigen-specific Treg cells and a reduction in cytokine production by Th1 and Th2 cells. Although no direct evidence that changes in antigen-specific Treg responses are responsible for disease prevention has yet been provided, these studies suggest that novel therapeutic approaches based on the enhancement of the Treg population in atherosclerosis might be feasible.
Other strategies exist to expand Treg numbers. Antibodies directed against the T-cell marker CD3 can reconstitute self-tolerance in established autoimmune diseases, such as type 1 diabetes mellitus [139]. Intravenous or oral anti-CD3 therapy reduced atherosclerotic lesion development in Ldlr$^{-/-}$ mice [140]. This beneficial effect was associated with enhanced TGF-β and Foxp3 mRNA expression in lymphoid organs, as well as with an increase in the subset of Treg cells that expressed latency-associated peptide [141].
Treatment with low dose IL-2 promoted Treg recovery and clinical improvement in patients with autoimmune vasculitis [142]. In Apoe$^{-/-}$ mice, functional delivery of IL-2 to pre-established atherosclerotic lesions [143] or IL-2/anti-IL-2 mAb (JES6-1) treatment [144, 145] resulted in plaque reduction mediated by Treg expansion.
On the basis of studies demonstrating that calcitriol, an active form of vitamin D3, can induce tolerogenic immune responses, calcitriol has been orally administered to Apoe$^{-/-}$ mice to induce Treg and tolerogenic DCs, which was accompanied by slower progression of atherosclerosis [146].
The measles virus is known to suppress the immune system through inhibition of dendritic cell activation, decreased IL-12 production, and reduced effector-Th-cell proliferation [147]. Apoe$^{-/-}$ mice treated with nucleoprotein from the measles virus had a marked inhibition of atherosclerosis and promotion of a Tr1-cell response [148]. Mycobacterium bovis BCG killed by extended freeze-drying injected to Apoe$^{-/-}$ or Ldlr$^{-/-}$mice showed atheroprotective effects through IL-10 production and Treg cell expansion [149].

NKT cells

NKT cells are a distinct subset of T-cells expressing both natural killer and T-cell markers. Unlike T-cells, which recognize peptide antigen presented by MHC molecules, NKT cells recognize lipid antigens presented by the hydrophobic MHC-like molecule, CD1d expressed on APCs. One of the well-studied and the major subset of NKT cells is type 1, also called invariant NKT-cells (iNKT), which are characterized by an invariant TCRα chain (Vα24Jα18) paired with one of a small number of TCRβ chains. iNKT-cells play a major role in bridging the innate and adaptive immune responses. They are constantly activated and respond immediately upon antigen encounter.

To elucidate the direct role of NKT cells in atherosclerosis, mouse models of CD1d deficiency were used. These mice lack both variant and invariant NKT-cells. NKT cells were also selectively activated by using the synthetic glycolipid α-galactosylceramide (α-Galcer). Both chronic deficiency ($CD1d^{-/-}$) and acute activation of NKT cells in $Apoe^{-/-}$ or $Ldlr^{-/-}$ mice confirmed their pro-atherogenic effects [150-152]. However, this effect was observed only in the early but not in the advanced stages of atherosclerosis [151, 153]. Adoptive transfer of splenocytes from NKT-cell enriched Vα14Jα18 TCR transgenic mice in $Rag^{-/-}Apoe^{-/-}$ mice resulted in increased atherosclerotic lesions compared to recipients transplanted with NKT cell deficient splenocytes [154]. $Jα18^{-/-}Ldlr^{-/-}$ mice that are depleted in iNKT cells had markedly reduced atherosclerosis and IFN-γ expression in lesions [155]. Altogether these studies indicate that NKT cells are pro-atherogenic. However, in one study, activation of NKT cells by α-Galcer (combined i.p. and i.v.administration) reduced lesions in a model of collar-induced carotid atherosclerosis in $Ldlr^{-/-}$ mice, while no effect was found in $Apoe^{-/-}$ mice [156]. In this model, α-Galcer administration in $LDLr^{-/-}$ mice, but not in $apoE^{-/-}$ mice, increased $CD3^+IL\text{-}10^+$ cells in spleen and mediastinal lymph nodes. No change in $CD3^+IFN\text{-}\gamma^+$ cells and $CD3^+IL\text{-}4^+$ cells was observed, while in other studies in which α-Galcer was proatherogenic, IL-4 and IFN-γ production increased [150-152], which could account for the discrepancy.

Given the proatherosclerotic role of NKT cells, therapeutic applications involving NKT cell depletion might have beneficial effects.

III. Role of B cells in atherosclerosis

III.1. B cell ontogeny

B cell characterization has been strongly improved during the last two decades with the identification of several distinct B cell subsets based on their origin and function. Conventional B-2 cells that form the dominant B cell population in adult spleen (>85%) and lymph nodes include $CD5^-CD19^+CD23^+CD43^-IgM^{low}IgD^{high}$ Follicular (F) B cells and $CD5^-CD19^+CD23^-CD43^-IgM^{high}IgD^{low}$ Marginal Zone (MZ) B cells. B-2 cells originate from bone marrow precursors and contribute to T-cell dependent humoral and adaptive immune responses. B-2 cell responses are highly specific but delayed [157].

A minor population of B cells, B-1 cells, has been described in different organs, mainly in the spleen (5%) and the peritoneal/pleural cavities. The B-1 cell population derives from splanchno-pleural area and fetal liver, and differentiates into $CD5^+CD19^+CD23^-CD43^+IgM^{high}IgD^{low}$ B-1a and $CD5^-CD19^+CD23^-CD43^+IgM^{high}IgD^{low}$ B-1b cells in mice [158]. Unlike B-1b cells, B-1a cells are less efficiently reconstituted from bone marrow progenitors and may differ in terms of immunoglobulin structure, V_H usage and repertoire selection when they originate from B-1 cell-restricted bone marrow precursors [158, 159, 160]. There are several substantial differences between B-1 cells and other B cells [157, 159]. Briefly, B-1 cells are long-lived, non-circulating lymphocytes and have reduced antigen diversity and affinity compared to B-2 cells. B-1 mediated-immune responses are rapid but poorly specific. B-1a cells secrete natural IgM antibodies, which contribute to T-cell independent humoral immune responses. The low affinity antibodies produced by B-1a cells are polyreactive and constitute the first line of defense against bacterial pathogens, with a major proportion reacting with oxidized lipid moieties [4].

Although earlier studies had already reported immunosuppressive properties of B cells, the existence of a specific B cell subpopulation with regulatory properties (Breg) was only recently demonstrated [161]. At this moment a clear characterization of the Breg population is still lacking

since Breg cells share some functional (IL-10 production) and phenotypical ($CD19^+CD5^+$) characteristics with B-1a cells or MZB cells [161, 162]. A new subset of B-1a cells, innate response activator (IRA) B cells, has been recently identified [163]. B-1a cells migrate from the peritoneal cavity to the spleen where they develop into IRA B cells and produce granulocyte-macrophage colony-stimulating factor (GM-CSF) [163, 164].

III.2. B cell infiltration in atherosclerotic lesions

B cells have been identified at different stages in mouse atherosclerotic lesions [165, 166], but only in advanced plaques in humans [167, 168]. By immunohistochemistry, mature $CD22^+$ or $CD20^+$ B cells have been detected in both intima and adventitia of human atherosclerotic plaques. A recent report concluded that these B cells are most likely B2-derived plasmablasts, with evidence of local affinity maturation occurring in both adventitia and plaque, and the presence of a limited number of class-switched clones [169]. However, in old $Apoe^{-/-}$ mice, $CD19^+$B cells mainly accumulated in the adventitia close to advanced lesions with a nodular organization, called tertiary lymphoid organs (TLOs) [167, 170]. B cells were the major cells populating aortic TLOs, which contrasts with their minor presence (compared to T-cells and macrophages) within atherosclerotic plaques. These aortic TLOs develop close to the abdominal aorta and could be important for the generation of local humoral responses [171]. CCR-6 is required for B cell homing to the aorta [165]. Aortic TLOs are not present in early lesions in young $Apoe^{-/-}$ mice, but develop in old animals [171] with advanced lesions, suggesting a specific role in the progression of atherosclerosis rather than in the initiation of the disease.

III.3. Humoral B cell responses

Initially, the role of B cells was confined to humoral immunity and most of the studies in the field of atherosclerosis focused on the characterization of anti-oxLDL antibodies and elucidation of their functions. Immunization strategies have been developed by several groups to investigate the role of the anti-oxLDL antibodies, in the hope to develop new therapeutic strategies to combat atherosclerosis.

IgM antibodies

B-1 cells secrete natural antibodies that are predominantly IgM and IgA. Both are present during the first stage of life despite no contact with foreign antigens, like in the case of gnotobiotic mice bred in a completely sterile environment [172]. Naive B-1 cells produce most of the plasma IgM antibodies and after contact with antigens proliferate and secrete more IgM molecules. Direct experimental evidence supporting an atheroprotective role for natural antibodies first came from studies showing that $Ldlr^{-/-}$ mice deficient in soluble IgM, that express but cannot secrete IgM, developed larger atherosclerotic lesions compared to wild type $Ldlr^{-/-}$ mice [173]. In humans, levels of plasma IgM against oxLDL are inversely related to atherosclerotic plaque size [174] and to ischemic cardiovascular events [175]. 30% of all plasma IgM in human and mouse bind to oxidation specific epitopes (OSE) [4]. The prototype of such IgM is the EO6 IgM that was identified from a panel of $Apoe^{-/-}$ mice hybridoma, and was characterized by its ability to bind to phosphorylcholine (PC) [176] present on oxLDL, apoptotic cells, as well as on certain microbial antigens (reviewed in [2]). EO6 had 100% homology with the germ-line encoded T15 antibody that covalently binds to PC present on the capsule of pathogens [177]. These EO6/T15 antibodies may contribute to the elimination of oxLDL and apoptotic cells, as well as to the defense against *Streptococcus pneumoniae*. Interestingly, splenectomized patients have increased susceptibility not only to pneumococcal infections but also to CAD [178].

Immunization protocols in animal models were subsequently used to investigate the role of natural antibodies in atherosclerosis. Immunization of high-fat diet-fed $Ldlr^{-/-}$ mice with heat-inactivated PC-rich pneumococci [179] induced high titers of plasma anti-oxLDL IgM (predominantly EO6) and significantly reduced atherosclerosis. Immunization with oxLDL in both atherosclerotic rabbits [180-182] and mice [75, 183, 184] also generated high titers of antibodies and reduced atherosclerosis development. Interestingly, immunization with malondialdehyde (MDA)-LDL that does not contain PC-exposing oxidized phospholipids induced T15/EO6 antibodies to levels higher than those found in non-immunized mice fed a high-fat diet [75].

Immunological analysis revealed that MDA-LDL immunization induced a Th2 polarization with a production of IL-5 that promoted B1 antibody production. Convincing experiments showed that T15/EO6 circulating antibodies were not detectable in IL-5$^{-/-}$ mice and did not increase after MDA-LDL immunization. Moreover, IL-5 deficiency in Ldlr$^{-/-}$ mice exacerbated atherosclerosis [179]. Intriguingly, immunization with native LDL elicited the same level of protection as oxLDL immunization [185]. Yet, only MDA-LDL immunization yielded high titers of antibodies against OSE, suggesting that the antiatherogenic effect of immunization does not primarily depend on the production of IgM antibodies against OSE, but more likely results from the activation of cellular immune responses.
In vivo experiments demonstrated the atheroprotective activity of T15/EO6 natural antibodies, but the underlying mechanisms remained unknown. In vitro, EO6/T15 bound to the oxidized epitopes (lipid and ApoB) of LDL and inhibited their uptake by macrophage scavenger receptors [186], specifically CD36 and scavenger receptor class B type I (SR-BI) [187, 188]. IgM antibodies have been detected in atherosclerotic lesions, colocalizing with macrophage-rich area [173]. T15/EO6 IgM also bind to oxidized phospholipid-rich apoptotic cells and block their pro-inflammatory properties, including endothelial cell activation [189]. Moreover, T15/EO6 may promote the clearance of apoptotic cells that accumulate within advanced atherosclerotic lesions and participate to the growth of the necrotic core [190]. Finally, a hypothesis based on the binding of IgM with minimally oxLDL that prevent LDL entering into vulnerable sites was proposed but not confirmed in experiments that measured the clearance rates of infused oxLDL in mice. No difference in the rate of clearance of oxLDL from the plasma was observed between immunocompetent Apoe$^{-/-}$ mice and Rag$^{-/-}$Apoe$^{-/-}$ mice that lack antibodies [191].

IgG antibodies
IgG is a family of molecules comprised of four members in mice (IgG1, IgG2a, IgG2b, and IgG2c/IgG3) and humans (IgG1, IgG2, IgG3, and IgG4). IgG antibodies are produced by B-2 cells in a Th cell-dependent manner. Th1 and Th2 cells specifically activate mature B cells to produce IgG2a and IgG1 subclasses, respectively [192]. IFN-γ is required for IgG2a and IgG3 production [193], and IL-4 for IgG1. Numerous studies have reported that B-2 cells respond to atherosclerosis-associated antigens and produce IgG antibodies. Yet, the distinction between antibody-mediated and cellular-mediated effects of B-2 cells on atherosclerosis is difficult to define in a precise manner. IgG antibodies reacting against OSE have been detected in the plasma and vascular lesions of both patients with CAD and animal models of atherosclerosis [4, 194]. In Ldlr$^{-/-}$ mice, a correlation has been reported between titers of IgG against oxLDL and lesion progression [195]. In humans, results about the relation between anti-oxLDL IgG molecules and CAD are conflicting. In some studies a positive correlation was reported [196-198] whereas a negative relationship was found in some others [199]. In animal models, immunization protocols using MDA-modified LDL led to increased titers of IgG against OSE and a reduction of atherosclerotic lesions [180]. The inhibition of T-B cell interactions using an anti-OX40L blocking antibody resulted in reduced levels of anti-oxLDL IgG1 antibodies, increased levels of IgM and reduced atherosclerosis in Ldlr-/- mice [200].
While accumulating evidence has indicated that IgM antibodies against oxLDL are anti-atherogenic, the role of anti-oxLDL IgG antibodies has not yet been fully elucidated [2]. The difference in effect between these isotypes of oxLDL auto-antibodies on atherosclerosis could be partially accounted for by the different functions of the specific receptors to which the Fc fragment binds. Stimulation of type I Fc gamma receptors (FcγRI), which have high affinity for Th1-associated IgG2a [201], on macrophages has been shown to induce inflammatory responses [202], whereas engagement of FcγRIIb, with low affinity for Th2-associated IgG1 [201], elicited atheroprotection [203]. Interestingly, FcγR γ-chain deficiency in Apoe$^{-/-}$ mice protected against atherosclerosis due to the loss of FcγRI and FcγRIIIA, but not FcγRIIb [204].

III.4. Cellular B cell responses
B cells have classically been thought to contribute to the immune response through differentiation into antibody-producing plasma cells. However, human and experimental studies have demonstrated that genetic or pharmacologic B-cell depletion can modulate T-

cell-mediated auto-immune diseases independently of B-cell antibody production, including type 1 diabetes and rheumatoid arthritis, which suggests that the cellular functions of B cells are important in the regulation of the adaptive immune response [205]. B cells, in addition to producing antibodies, also secrete cytokines [206]. For example, B cell-derived lymphotoxin α (LT α) and TNF-α control the development of follicular DCs and the formation of B cell follicles in the spleen. Also, in the context of myocardial infarction, B cells can release CCL7/MCP-3 that stimulates the mobization of monocytes from the bone marrow into the circulation [207].

In an attempt to explore the role of B cells in atherosclerosis, splenectomy was performed in Apoe$^{-/-}$ mice [208]. This led to a reduction of T- and B-cell pools, associated with accelerated atherosclerosis. In addition, transfer of splenic B cells from Apoe$^{-/-}$ mice reversed the vascular phenotype, suggesting a protective role of mature B cells. This finding was supported by data showing that bone marrow transplantation from μMT mice, deficient in B cells, into Ldlr$^{-/-}$ mice increased atherosclerosis [209]. Intriguingly, a reduction of T cell activation was also observed in this study. Even though these studies document an atheroprotective role of B cells, it was not clear whether this was mediated through cellular or humoral responses.

Recent studies allowed us to better understand the role of humoral and cellular functions of B cells in atherosclerosis. Experimental protocols based on anti-CD20 depleting antibody administration induced a marked and prolonged depletion in mature B cells (more than 95% in the spleen, the blood and the lymph nodes) with little effect on B-1 cells in the peritoneal cavity of atherosclerosis-prone mice [210]. The depletion of B cells led to decreased atherosclerotic lesions in Apoe$^{-/-}$ and Ldlr$^{-/-}$ mice fed a chow or high fat diet [210, 211]. Plasma levels of natural IgM were unchanged following B-cell depletion, likely due to minimal depletion of peritoneal B-1a cells, but the titers of IgG antibodies against oxLDL were markedly reduced. Moreover, B-cell depletion also reduced activation and proliferation of DCs and CD4$^+$ T cells, which was associated with decreased IFN-γ but increased IL-17 production [210]. Transfer of purified B-2 cells increased titers of IgG antibodies and atherosclerotic lesions, whereas B-1a transfer restored natural IgM antibody pool and reduced atherosclerosis [210, 211]. The transfer of B-1a cells from sIgM$^{-/-}$ mice did not protect against atherosclerosis, confirming that the protective effect of B-1a cells was mediated by IgM. Of note, transfer of B-1a cells also diminished the accumulation of apoptotic cells within atherosclerotic plaques, in agreement with the role of natural IgM antibodies in the clearance of dead cells [212]. B cell-activating factor (BAFF)/BAFF receptor (BAFFr) interactions are important for B cell survival and maturation. BAFF receptor deletion selectively depletes B-2 cells, with no effect on B-1 cells, and reduces T cell activation. The transfer of bone marrow from BAFFr deficient mice into Ldlr$^{-/-}$ mice reduced atherosclerosis, which confirms the proatherogenic activity of mature B-2 cells [213]. More recently, a proatherogenic role has been attributed to the newly identified IRA B cells by promoting the expansion of classical DCs and Th1 polarization [164].

Recent important advances have extended our knowledge of the role of B cells in atherosclerosis, underscoring the protective function of B-1a cells through IgM secretion and the pathogenic effect of B-2 and IRA B cells that amplify the immune-inflammatory response through T cell activation and Th1 polarization (Figure 3). New therapeutic strategies based on B-1a cell expansion or B-2 depletion could be designed in the future to combat atherosclerosis.

IV. Role of Dendritic cells in atherosclerosis

DCs are the most important APCs that drive the maturation and polarization of naive T cells recognizing specific MHC-presented antigenic peptides, with the nature of the T cell response dependent on DC status determined by signals received by pattern recognition receptors, membrane-bound costimulation and cytokines [214]. Immature DCs, phenotypically characterized by the expression of few costimulatory molecules induce T cell death, anergy, or skewed differentiation toward a regulatory phenotype [215], thus can also be thought of as "tolerogenic". In addition to immature DCs, mature or activated DCs receiving strong anti-inflammatory signals such as TGF-β or IL-10 are also tolerogenic, thus the T cell stimulatory capacity of DCs is not as simple as an immature/mature dichotomy. DCs are also instrumental in defining the type of effector T cell formed. For example, IL-12 produced by DCs is central in

Th1 differentiation whereas IL-6 promotes a Th-17 response [216]. The activation of both effector and memory T cells is not restricted to DCs, however, and involves other APCs such as B cells and macrophages [217].

IV.1. DC ontogeny and subsets in atherosclerosis

DCs originate from $CD34^+$ bone marrow precursors of the myeloid lineage (common myeloid precursors (CMPs)) [218, 219]. Immature DCs circulate via the bloodstream and populate tissues, mainly close to epithelial and body cavity surfaces, where they serve as sentinels of infection or injury [220]. In general terms, the different sublineages of DCs found in mice and humans are now well characterized [221, 222], although debate and blurring of phenotypes remains between monocyte-derived "macrophages" and "DCs" in inflammatory tissue such as atherosclerotic plaque. DCs, defined by their primary function of presenting antigen to T cells, have 3 major precursors in the blood (Figure 4): Fms-like tyrosine kinase 3 $(Flt3)^+$ pre-classical DCs (cDCs), colony-stimulating factor 1 receptor $(CSF1R)^+$ monocytes and $Flt3^+$ plasmacytoid DCs (pDCs), with both $Flt3^+$ populations originating from a common dendritic precursor (CDP) that arises from CMPs [223, 224]. Transcription factors influencing these lineages include Zbtb46 and BATF3 for pre-cDCs [221] and Tcf4 for pDCs [225, 226]. Pre-cDCs directly entering lymphoid tissue become specialized lymphoid resident DCs. Pre-cDCs entering peripheral tissues are classed as migratory DCs that are the classic sentinels that sample antigen and once activated by innate signals, such as TLR ligands, migrate to draining lymph nodes enabling interactions with multiple T cells. In both cases, pre-cDCs differentiate into $CD103^+$ ($CD8^+$ in lymphoid tissue) and $CD11b^+$ (or $CD4^+$) cDC subsets. Monocytes, in addition to becoming macrophages of various mature phenotypes, can form $CD11b^+$ DCs that express DC associated antigens such as DC-SIGN and possess high T cell stimulatory but low phagocytic capacity [227]. Defining monocyte-derived cells as macrophages or DCs and functional subsets thereof is a subject of much debate.

In the context of understanding links with adaptive immunity, myeloid cells of several phenotypes express significant levels of MHCII [227, 228] and thus likely contribute to T cell activation within atherosclerotic plaques. Although CD11c is expressed by nearly all plaque monocyte-derived cells, the presence of $CD11c^+$ cells negative for expression of macrophage markers such as CD68 and F4/80 suggests the presence of distinct myeloid DCs [227, 228]. Zbtb46 is a transcription factor expressed by monocyte-derived DCs and cDCs, but not macrophages or pDCs [221] and represents an important novel marker to aid in understanding plaque myeloid subsets. Recently, a subset of $CCL17^+$ DCs that express high levels of co-stimulatory molecules (CD40, CD80, CD86) has been described within the atherosclerotic plaque but its specific origin remains unclear [127]. Transcription factor E2-2 effectively differentiates pDCs from other DC subsets, as does the surface marker Siglec-H [225]. The most well characterized function of pDCs is to rapidly produce large amounts of type-I IFN in response to viral infection. However they can also take on mature cDC-like phenotypes and regulate T cell responses via antigen presentation [229] and promote Treg function through indoleamine 2,3-dioxygenase (IDO) [230]. A growing literature has identified significant contributions of pDCs to autoimmune diseases in addition to viral infections.

In normal arteries, DCs were identified [231] along the subendothelial intima layer and also in the adventitia, close to the vasa vasorum [232]. In atherosclerosis-prone regions, such as the lesser curvature of the aortic arch, DCs are present in higher numbers [227, 233-235] including $CD11c^+CD11b^-CD103^+$ DCs derived from pre-cDC and $CD11c^+CD11b^+CD103^-$DCs derived from monocytes [227]. This last subset accounts for the majority of $CD11c^+$ cells in more advanced plaques and likely originates from circulating monocyte precursors [227]. Mature DC accumulate in mouse and human atherosclerotic lesions with a marked increase in advanced stages and in complicated plaques [236]. DCs also accumulate in adventitial TLOs [171]. pDCs are present in human and mouse atherosclerotic plaque in small numbers [230, 237, 238]. It is also possible that since in some activation contexts pDCs become cDC-like in phenotype, further pDC-derived cells exist in plaques. Indeed in general, all DC subsets converge in terms of transcriptional profile in response to multiple activation signals [239]. Thus, DCs with various

ontogeny and surface phenotype are present throughout the natural history of plaque development.

IV.2. Functional roles for DCs in atherosclerosis

An unexpected finding resulting from studies manipulating DC numbers has been the effects on cholesterol homeostasis, precluding unequivocal conclusions on the influences of their immune functions in atherosclerosis. Depleting $CD11c^+$ cells in CD11c-DTR mice led to enhanced cholesterol levels and no change in atherosclerosis, an interpretation of which is that higher cholesterol but lower DC-driven T cell immunity cancel each other out [240]. Enhanced macrophage apoptosis had a similar effect [241]. Another study with the same mice reported that these mice also develop a progressive myeloproliferative state, suggesting indirect effects on the hematopoietic system with prolonged depletion of peripheral cDCs [242]. Conversely, prolonging $CD11c^+$ cell survival by Bcl2 overexpression had the opposite effects on cholesterol and also did not change atherosclerosis [240]. Intimal DCs were shown to form foam cells in the aortic intima [243] and using CD11c-DTR mice in very short term high fat diet experiments, the lack of these intimal DCs dramatically reduced the lipid area, suggesting that DCs may be instrumental in the first stages of atherosclerosis. Overall, these studies failed to demonstrate DC antigen presentation function as pro-atherogenic, as has long been hypothesized, whereas Koltsova et al demonstrated that, ex vivo, aorta resident APCs can promote TNF-α and IFN-γ production by T cells from $Apoe^{-/-}$ but not WT mice [228]. Alternative approaches will be necessary to target this aspect more specifically. In contrast, a number of studies now highlight an important role for cDCs in maintaining anti-atherosclerotic regulatory T cells. (Figure 4). Regulatory T cell survival and hometostatic proliferation critically depend on continued interactions with APCs, presumably presenting the relevant autoantigen in a tolerogenic context. For example, blocking DC maturation through CD11c-specific knockdown of MyD88 altered the Treg cell pool and accelerated atherosclerosis [244]. This is further supported by experiments showing that lack of ICOS or PD-1, inhibitory pathways of the TNF superfamily, reduce Treg cell capacity and lead to increased atherosclerosis, as does treatment with CTLA4-Ig (Abatacept) [245, 246], which disrupts CD28-CD80/86 interactions. In terms of defining which subsets of cDCs are involved, Choi et al demonstrate that the majority of $Flt3^+$ pre-cDC derived cells in normal and atherosclerotic plaques are $CD103^+$ DCs and that Flt3 deficiency increases atheorsclerosis [227], whereas $CCL17^+$ DCs prevent the differentiation of naïve T cells into Treg cells through CCR4 and thus promote atherosclerosis [127]. Combining these studies leads to the conclusion that $CD103^+$ cDC MyD88 signaling is vital for maintaining regulatory T cells and that this is antagonized in atherosclerosis by the induction of $CCL17^+$ $CD11b^+$ cDCs. The signals that lead to DC maturation in atherosclerotic lesions remain unknown, but numerous candidates include inflammatory cytokines, TLR ligands, nuclear fragments derived from necrotic cells and (oxidized) lipids. The multiple roles of TLRs and their ligands in atherosclerosis are reviewed in detail elsewhere [247, 248]. In vitro, oxLDL strongly modifies human DC phenotype with an up-regulation of surface T cell-stimulatory molecules (CD40, CD86 and HLA-DR), scavenger receptor expression (CD36) and increased cytokine production [249, 250]. Systemically, though, T cell responses to exogenous immunization were not changed in hypercholesterolemic conditions [251]. DC and MHCII co-localization [252] and frequent contacts between DCs and T cells observed within the atherosclerotic plaques suggest local interactions and specific T cell stimulation [236] (Figure 4). Indeed, $CD11c^+$ cells present in aortic explants interact in an antigen-specific manner with exogenously added T cells [253]. Data from animal models show that genetic deletion of important co-stimulatory molecules (CD80/CD86) in mice reduces T cell activation/infiltration and reduces atherosclerosis [254]. The inability of $CD11c^+$ cells to respond to anti-inflammatory TGF-β signaling due to conditional deficiency in TGF-BRII leads to enhanced TNF and IL-12 production by DCs and increased atherosclerosis [255]. pDCs are a major source of pro-atherogenic type I IFN, but their role in atherosclerosis is still under debate as the depletion using an antibody against bone marrow stromal cell antigen-2 (BST-2/PDCA1) had opposite effects on $Ldlr^{-/-}$ and $Apoe^{-/-}$ mouse models of atherosclerosis [230, 237, 238], and this antigen is not entirely pDC-specific. Nevertheless, a potentially important role is indicated and deserves further attention, especially since alternative genetic approaches

are now available, including pDC specific DTR transgenic mice [256] and pDC deficient mice [225]. The latter mice, which lack the E2-2 transcription factor critical for pDC differentiation only in DCs, interestingly highlight the ability of pDCs to become cDC-like cells, which has been reported to also occur in a number of infection and autoimmune contexts. Given that the existing studies on pDC roles in atherosclerosis each highlighted distinct molecular mechanisms, it will be important to further explore pDC functions beyond type I IFN production, such as antigen presentation [238] or Treg stimulation via IDO [230].

The central role of DCs in the modulation of the adaptive immune response has been illustrated by DC-based vaccination strategies against atherosclerosis, showing that intravenous injection of oxLDL-loaded DCs in mice induced an attenuation of flow-induced atherosclerosis and a stabilization of plaque phenotype in carotid arteries [257]. Also, transfer of DCs loaded with ApoB-100-derived peptides and incubated with IL-10, known to induce a tolerogenic phenotype led reduced atherosclerosis as well as the systemic and local inflammatory responses in human ApoB-100-transgenic $Ldlr^{-/-}$ mice [258]. These pre-clinical studies suggest that DC-based vaccination could represent a new approach to treat atherosclerosis.

V. Unresolved questions

In atherosclerosis, the precise site of DC-mediated antigen presentation to T cells remains unknown. The identification of oligoclonal T cell infiltration in human atherosclerotic plaques [40] and the frequent contacts between T and DCs within the lesions [236] raised the hypothesis of direct antigen presentation in the vascular wall. Using a model of live-cell imaging on explanted aorta from mice, these DC-T cell interactions were visualized in the adventitia [253]. Interestingly, T cells isolated from hypercholesterolemic animals interacted in vitro with adventitial APCs to a much greater extent than T cells from naive BL6 mice, providing evidence for atherosclerosis antigen-specific T cells and the possibility of local presentation of those antigens by vascular wall APCs. However, there is still no information whether this happens in vivo and where naive T cells are sensitized. What this observation suggests is that DCs might interact with effector or memory T cells in the vascular wall, but not with naive T cells. Yet, the site of initial antigen encounter is still unknown for both DCs and T cells, with several viable possibilities. DCs might take up antigen(s) in lesions and migrate to lymph nodes, or they might ingest circulating antigens (i.e., in spleen) for effective antigen presentation. Morever, it is unclear whether T cells are primed in lymph nodes or spleen, or in TLOs. Indeed, despite abundant levels found in plaques, both oxLDL and Hsp65 can be found in the blood and are also likely to be present at high concentrations in lymph leaving plaque and entering the draining adventitial lymphatics [259]. Although many myeloid cells may not ever leave plaques at advanced stages [260], some DC departure dependent on Ccl21-Ccr7 chemotaxis is possible [261, 262]. DCs in the adventitia could also act as migratory DCs, or could conceivably present antigen in situ. Whether naïve T cells can exit capillaries and interact with DCs in the adventitia is unknown. However, since the adventitia is a site of future tertiary lymphoid tissue, this is an intriguing possibility. Circulating antigen could alternatively be taken up by resident lymphoid DCs, particularly, for example, if complexed with low affinity antibodies produced by innate B cells.

DC trafficking is another topic of controversy. Experiments using aortic transplantation in mice identified CCR7 and its ligands CCL-19/CCL-20 as an important regulator of DC emigration from the atherosclerotic lesion [261]. However, in a model of atherosclerosis regression, the emigration of myeloid cells was not affected by CCR7 deficiency [260].

Specific antigen-driven T cell immunity in atherosclerosis

Adaptive immunity is an intelligent response against selective (auto)antigens, and the oligoclonal TCR repertoire of T cells that infiltrate human atherosclerotic plaque argues for the selectivity of the adaptive immune response in atherosclerosis. However, definitive identification of these antigens remains unsolved. Two serious candidates have been proposed based on human and experimental studies, Hsp60 and LDL-associated peptides. Hsp are cytosolic, highly conserved molecular chaperones involved in several auto-immune diseases such as multiple sclerosis or rheumatoid arthritis [263], although they are also found extracellularly in chronic inflammatory tissues. Hsp60 has been detected by

immunohistochemical staining in human atherosclerotic samples [264]. Immunization against Hsp65 in hypercholesterolemic rabbits induced Hsp-65-reactive T cells and accelerated atherosclerosis [265]. In Ldlr$^{-/-}$ mice, Hsp65 immunization also increased lesion size in the aortic sinus and T cell infiltration within the vascular wall [266]. Moreover, the transfer of T cell isolated from Hsp65-immunized mice accelerated atherosclerosis in Ldlr$^{-/-}$ animals [267]. In contrast, induction of tolerance by nasal administration of Hsp65 reduced atherosclerotic lesion size and T cell infiltration. This protocol strongly modulated CD4^{+} T cells in draining lymph nodes with a reduction of IFN-γ and increased IL-10, suggesting an expansion of Tr1-like Treg cells [133].

LDL-associated peptides represent another major source of putative autoantigens whose role has been highlighted by studies that explored the natural antibody response to oxLDL (reviewed in [2, 4]). T cells isolated from human plaques can proliferate in a MHCII-dependent manner in the presence of oxLDL [29]. More recently, T cell clones that recognize native oligopeptides of ApoB-100 protein were also reported [136]. Adoptive transfer of oxLDL-reactive T cells in Apoe$^{-/-}$ boosted Th1 immunity and accelerated atherosclerosis [268]. In contrast, other strategies focused on antigen-specific Treg cell expansion, including subcutaneous administration of low doses of ApoB-100 derived-peptides [138] or injection of ApoB-100-loaded DCs [136], have been shown to reduce the disease in Apoe$^{-/-}$ mice. Recently, ApoB-100 peptides characterized as having high affinity for MHCII were also effective in reducing atherosclerosis [269].

Mechanisms of self-tolerance normally inhibit the maturation and/or activation of T cells specific for LDL-associated peptides and Hsp60. There are several explanations why T-cell responses against normally tolerated self-proteins may occur. First, self-proteins modified *in vivo* by oxidation are recognized as non-self molecules [270]. Moreover, molecular mimicry between self-proteins and microbial particles could affect the discriminative functions of the immune system with bacteria-reactive T cells that target “by mistake” homologous self-proteins [271]. Finally, the environment surrounding antigen presentation could affect T-DC interactions. In the context of atherosclerosis, the accumulation of apoptotic cells generates membrane derived oxidized phospholipids or DNA fragments, which can be recognized by the innate immune system as DAMPs [272], leading to DC activation through pattern recognition receptors (TLRs or NODs) and resulting in break of tolerance to self antigens. As an example, the genetic invalidation of Mfge-8 or MertK, both proteins implicated in apoptotic cell clearance induced an accumulation of cell debris, activation of DCs and deviation of T cell responses toward a pro-atherogenic Th1 profile [190, 273, 274].

VI. Conclusion

Recent investigations of the immune responses in atherosclerosis have revealed a previously unappreciated complexity. Studies of immune-deficient mice on an atherosclerosis prone background have uncovered dual roles for the immune system in suppressing and promoting atherosclerosis. In these systems, the interplay of innate immunity, adaptive immunity and inflammation helps determine the outcome of the atherosclerotic process. Future work should aim at characterizing the immune pathways in patients with CAD to establish whether comparable alterations of immune functions contribute to atherosclerosis in humans. Immunological biomarkers that reflect T/B cell activation or Th cell polarization (Th1, Th2, Th17, Treg), predictive for the specific type of immune response should allow us to better define the immune phenotype of patients with CAD, and eventually improve stratification of patients with high cardiovascular risk. For instance, single nucleotide polymorphisms (SNPs) in several cytokine or immune-cell activation/signaling pathway genes have been reported. These SNPs might result in imbalance in Th cell polarization and contribute to clinical outcomes [275].

Therapeutic manipulations that are aimed at restoring defective immune functions, such as Treg or B-1 cell activity, or attenuating proatherogenic immune action, such as Th1, B-2 or IRA B cell activity, might reduce atherosclerosis development and progression. Taking into account the inter-individual diversity in the adaptive immune response would add to the benefit of current treatments of cardiovascular risk factors. Strategies for vaccination or tolerance

induction have already proven beneficial in animal models by stimulating B-1 activity and restoring Treg function, respectively. Molecules used in the treatment of autoimmune diseases such as anti-CD20 antibodies to deplete conventional B-2 cells, which protect against atherosclerosis in mice, may also benefit patients with CAD. The dual role of adaptive immunity in atherosclerosis further implies that immunotherapies should target several pathways. Combined approaches to both stimulate protective immune responses and inhibit pathogenic immune reactions are likely to prove most efficient.

Finally, a recent report showing that bacterial metabolites from commensal microorganisms regulate the immune system by promoting peripheral Treg cell expansion [276] open new avenues for studying the communication between microbiota, adaptive immunity and atherosclerosis.

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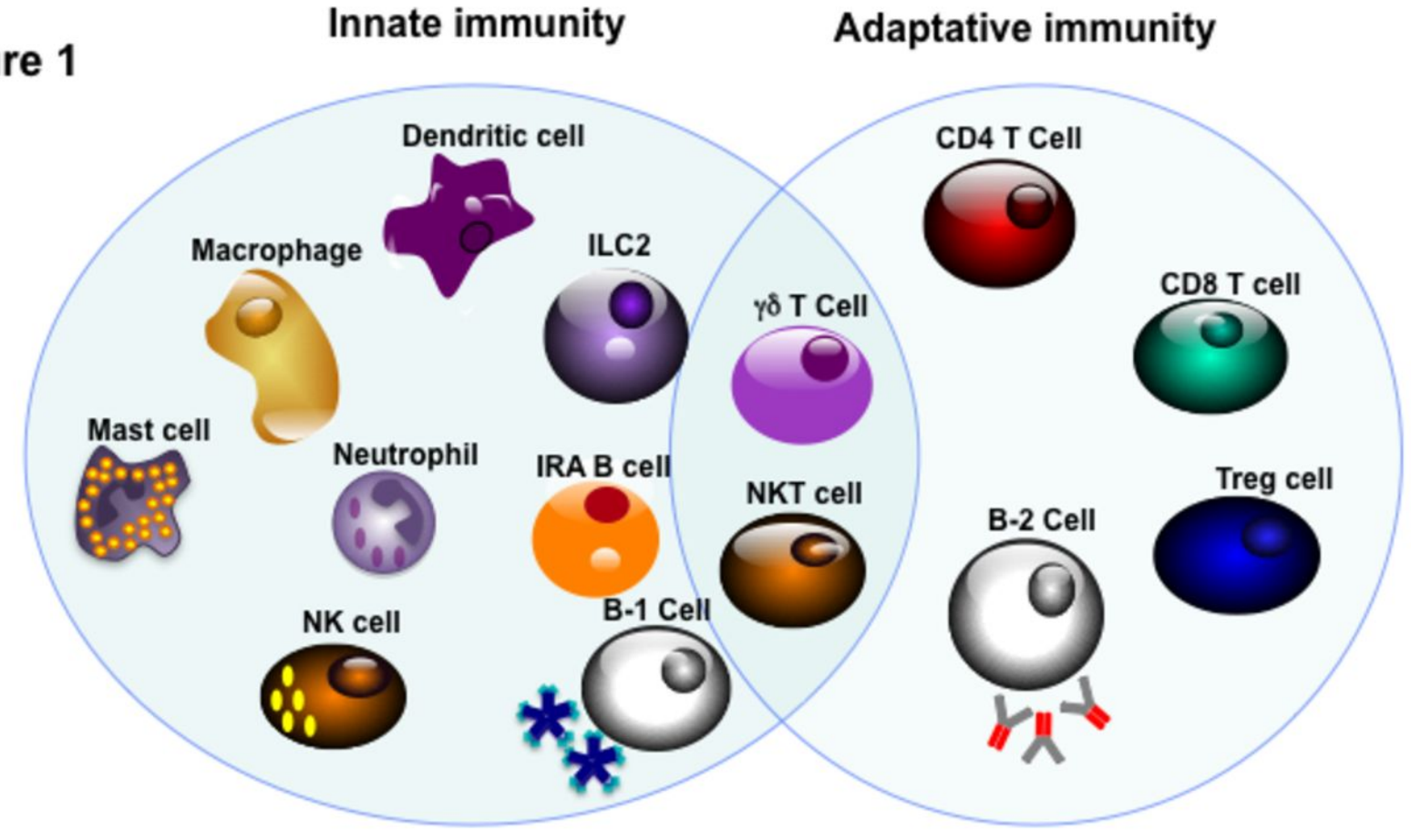
Figure 1. Innate and adaptive cellular response.
Innate immune cells are characterized by a rapid but poorly specific responses whereas daptive responses are more delayed but specifically recognize epitopes. Strong interactions between innate and adaptive systems have been highlighted during the last decade with several cell subsets positioned at the interface between both systems.
NK, Natural Killer; Treg, regulatory T cells; ILC2, Type 2 Innate Lymphoid Cells.; IRA B cell: innate response activator B cell

Figure 2. Differentiation, activation, and interactions between CD4+ T cell subsets.
Mature dendritic cells polarize naive Th0 cells into different effector T cells through antigen presentation to the TCR, secretion of cytokines and costimulation. Th1, Th2 or Th17 cells are categorized by the transcription factors they express and the cytokines they release. The archetypical cytokine of each subset is marked in bold. Tolerogenic dendritic cells prime Th0 cells toward a Treg phenotype. The complex interactions between the various CD4+T cell subsets involved in atherosclerosis are represented schematically.
DAMPs, Danger-associated molecular patterns; CTLA-4, cytotoxic T-lymphocyte antigen 4; Foxp3, forkhead box protein P3; IL, interleukin; ROR, RAR-related orphan receptor; STAT, signal transducer and activator of transcription; TBX21, T-box transcription factor TBX21 (also known as T-bet); TCR, T-cell receptor; MHC, Major histocompatibility complex; TGF-β 1, transforming growth factor β 1; Th , T-helper cell; TNF, tumor necrosis factor; IFN, Interferon; Treg, T-regulatory; Hsp, heat shock protein, oxLDL, oxidized low density lipoprotein.

Figure 3. **B cell responses in atherosclerosis.**
B-1a cells have been shown to be atheroprotective mainly through the release of anti-oxLDL antibodies. B-2 cells promote atherosclerosis, stimulate T/DC activation and Th1 polarization. IRA B cells secrete GM-CSF, promote DC expansion and Th1 polarization. Therapeutic strategies based on B-1a expansion (immunization protocol) or B-2 depletion (anti-CD20 antibody, Baff-R invalidation) have been shown to reduce atherosclerosis in experimental models.
BAFF, B-cell activating factor

Figure 4. Dendritic cell subsets in atherosclerosis. Dendritic cells in lymphoid organs and potentially vascular adventita derive from Flt3+ pre-cDCs directly from blood or migrating from peripheral tissues and form CD103+ or CD11b+ subsets. CD11b+ DCs also derive from monocytes and possibly pDCs. Flt3+ precursor derived CD103+ DCs maintain Tregs through multiple pathways including MyD88 dependent signaling and co-inhibitory interactions such as ICOS or PD-L1, whereas CCl17+ CD11b+ DCs suppress Tregs. CD80/86 and CD40 signaling as well as IL-12 production from mature DCs promotes naive T cell differentiation into pro-atherogenic Th1 cells. Within plaques, pre-cDC derived DCs are prominent foam cell-forming cells in very early lesions, whereas at later stagesmonocyte-derived DCs (and macrophages) recruit and activate proatherogenic Th1 cells through CCL17 production, antigen presentation and costimulatory signals.
cDC, conventional Dendritic Cell; pDC, plasmacytoid Dendritic Cell; ICOS, Inducible Costimulator; PD-L1, Programmed cell death ligand 1

Figure 1



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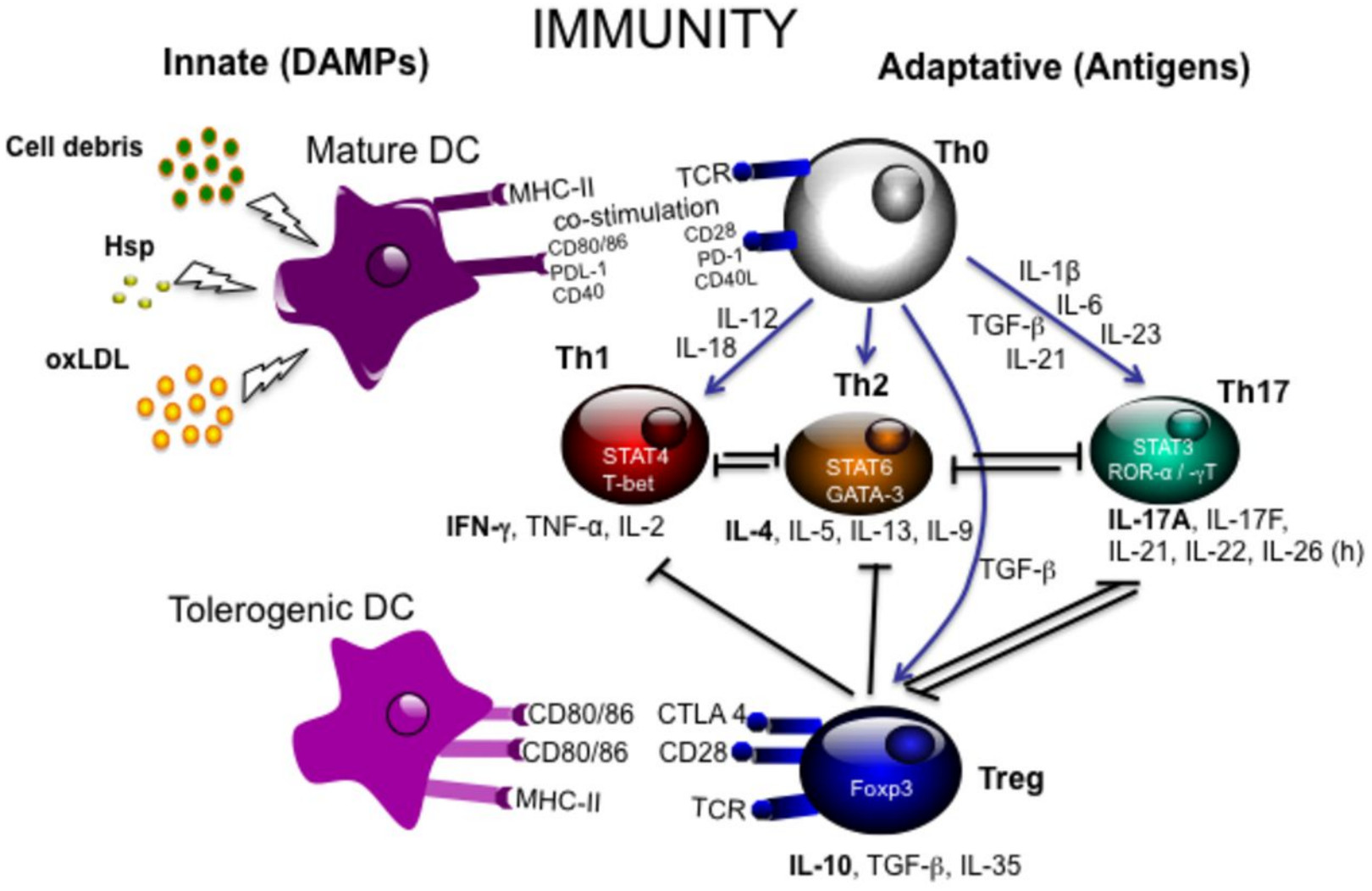
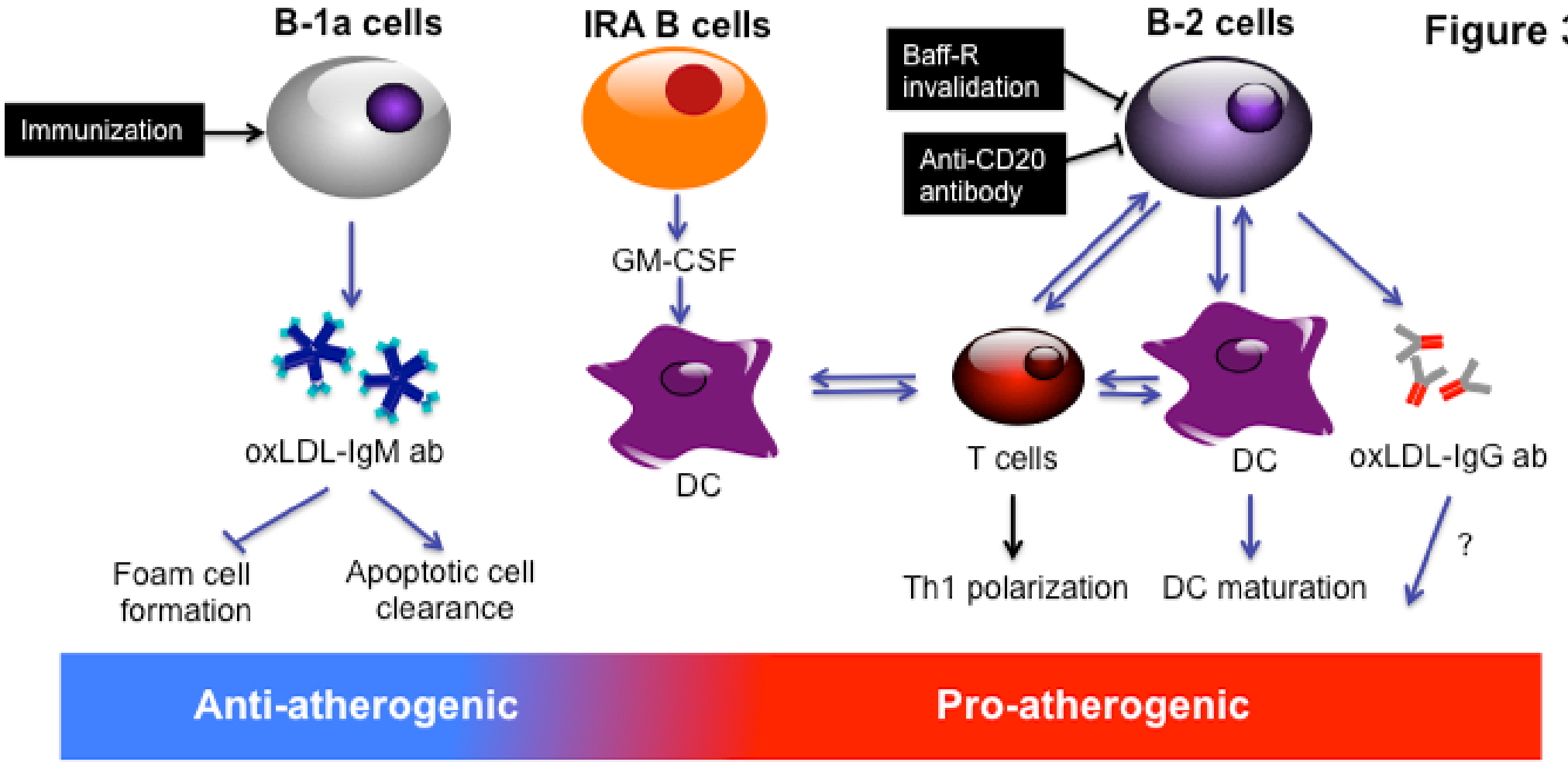

IMMUNITY
Innate (DAMPs)
Adaptative (Antigens)
Cell debris
Hsp
oxLDL
Mature DC
MHC-II
co-stimulation
CD80/86
PDL-1
CD40
TCR
CD28
PD-1
CD40L
Th0
IL-12
IL-18
Th1
Th2
IL-1β
IL-6
TGF-β
IL-21
IL-23
Th17
STAT4
T-bet
STAT6
GATA-3
STAT3
ROR-α / -γT
IFN-γ, TNF-α, IL-2
IL-4, IL-5, IL-13, IL-9
IL-17A, IL-17F,
IL-21, IL-22, IL-26 (h)
TGF-β
Tolerogenic DC
CD80/86
CD80/86
MHC-II
CTLA 4
CD28
TCR
Foxp3
Treg
IL-10, TGF-β, IL-35

Figure 2



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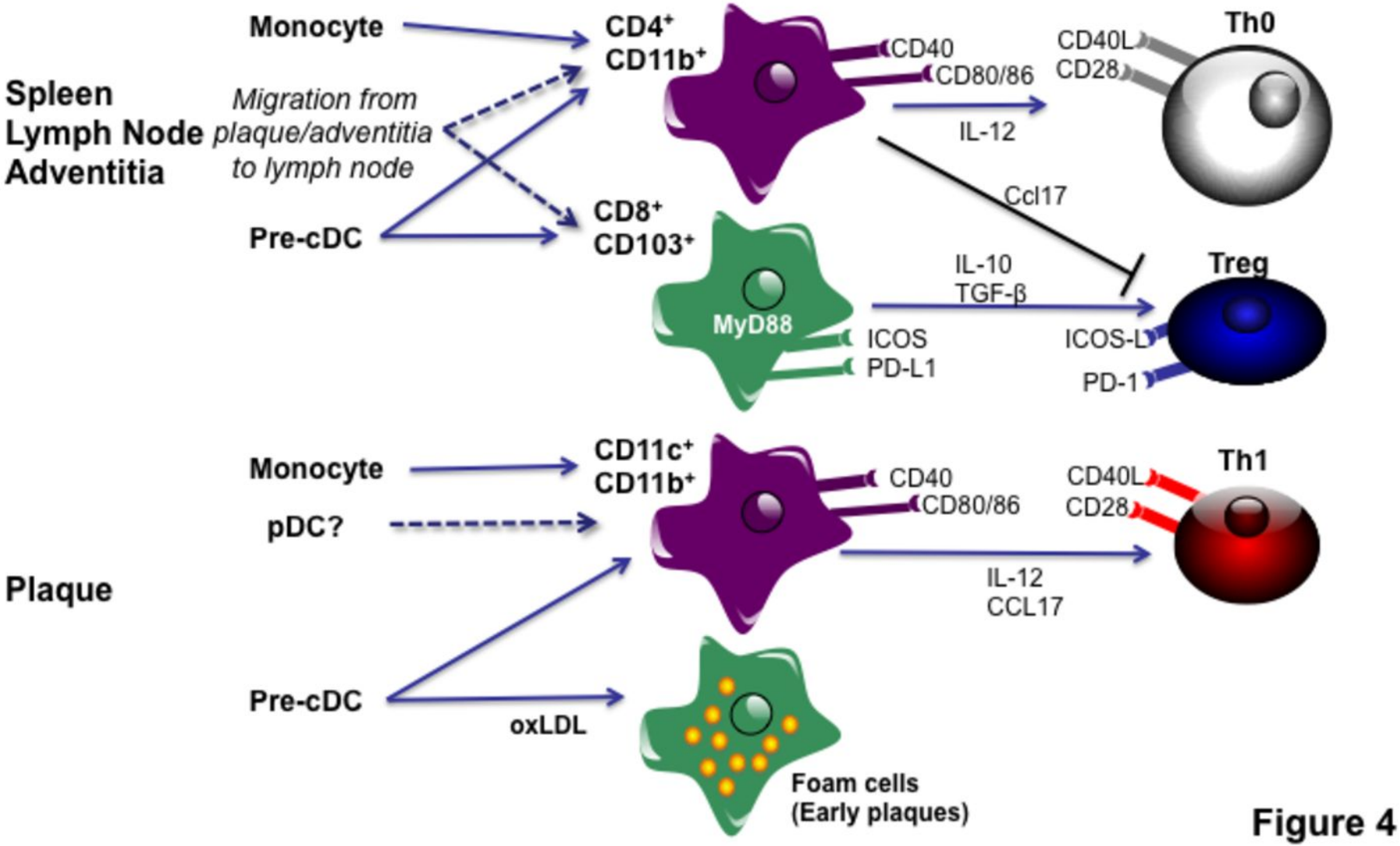
Spleen
Lymph Node
Adventitia
Monocyte
Migration from plaque/adventitia to lymph node
Pre-cDC
CD4+ CD11b+
CD8+ CD103+
CD40
CD80/86
IL-12
CD40L
CD28
Th0
Ccl17
IL-10
TGF-β
Treg
MyD88
ICOS
PD-L1
ICOS-L
PD-1
Plaque
Monocyte
pDC?
CD11c+ CD11b+
CD40
CD80/86
IL-12
CCL17
CD40L
CD28
Th1
Pre-cDC
oxLDL
Foam cells
(Early plaques)

Figure 4